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Kardiovaskularne bolesti i opstrukcijska apneja u snu

Cardiovascular diseases and obstructive sleep apnea

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SAŽETAK: *Prestanak disanja u snu predstavlja razmjerno čestu bolest koja pogađa oko 5% populacije. Javlja se kao posljedica kolapsa ždrijelne muskulature tijekom spavanja, uvijek u osoba koji hrču. Hipoksija, simpatička stimulacija, povećan oksidacijski stres, apoptoza, endotelna disfunkcija te smanjeni intratorakalni tlak, temeljni su patofiziološki otkloni koji prvenstveno pogađaju kardiovaskularni sustav. Intraktabilna arterijska hipertenzija, različite aritmije (fibrilacija atrija, ventrikulska tahikardija, sinusni zastoj ili AV blokovi), srčana ishemija ili infarkt, moždani udar, iznenadna srčana smrt, česti su u bolesnika s OAS. Posebno je česta u (gotovo svakog drugog!) bolesnika sa zatajivanjem srca. Dobra anamneza (trajna dnevna pospanost — česte prometne nezgode!) u adipoznih bolesnika, koji hrču u snu, s jednom od navedenih bolesti, treba buditi kliničku sumnju na opstrukcijsku apneju u snu. Konačna dijagnoza postavlja se polisomnografijom. Primjenom uređaja s kontinuirano-povećanim tlakom u dišnim putovima uspješno se liječi ova podmukla i potencijalno opasna bolest, koja, neliječena, ima lošu prognozu.*

KLJUČNE RIJEČI: *opstrukcijska apneja u snu, adipozitet.*

ABSTRACT: *Sleep apnea is a common medical condition that affects approximately 5% of the population. All patients with sleep apnea snore and experience pharyngeal airway collapse. Hypoxia, sympathetic stimulation, higher oxidative stress, apoptosis, endothelial dysfunction, and low intrathoracic pressure are the main mechanisms that cause sleep apnea and also affect the cardiovascular system. Therefore, resistant arterial hypertension, different arrhythmia (atrial fibrillation, ventricular tachycardia, sinus block or different types of AV blocks), myocardial ischemia and infarction, stroke or sudden cardiac death are all frequent medical conditions seen in sleep apnea patients. Moreover, chronic heart failure occurs in every other patient. Obese patients that snore and complain of day time sleepiness or have a history of frequent car accidents should have sleep apnea very high on their differential diagnosis list. Polysomnography is the test of choice to make the final diagnosis. The best results in treating this unusual and potential harmful disease are achieved by use of continuous positive airway pressure. Unfortunately, if left unrecognized and untreated, it can lead to serious medical conditions.*

KEYWORDS: *obstructive sleep apnea, obesity.*

Riječ je o prekidu disanja, u snu, do kojeg dolazi zbog kolapsa ždrijelne muskulature. Pogađa 5% pučanstva. Opstrukcijska apneja podrazumijeva prestanak disanja u trajanju od deset ili više sekunda, uz istovremene kontrakcije dišne muskulature, a opstrukcijska hipopneja znači nepotpuno prekinuto disanje, povezano s padom

Sleep apnea is caused by the larynx musculature collapse. It afflicts 5% of the population. Obstructive sleep apnea implies interruption in breathing lasting for some ten or more seconds, with simultaneous contractions of the breathing musculature, and the obstructive hypopnea implies incompletely interrupted breathing, related

saturacije kisika ili s buđenjem.[1] Dijagnoza opstrukcijske apneje u snu (OAS) postavlja se kad je apneja-hipopneja indeks (AHI) u satu veći od pet, uz izrazitu pospanost tijekom dana. Prema nekim izvorima u SAD-a čak više od 85% bolesnika koji boluju od ove bolesti ne znaju za nju![2] Može se, dakle, očekivati da je taj postotak još veći u RH!?

Povećani simpatički tonus, ponovljeni hipoksijski stres, oslobađa vazokonstrikcijske tvari, prvenstveno endotelin, i okidač je za oslobađanje medijatora upale poput interleukina-6, plazmatskog citokina ili C-reaktivnog proteina. Sve ovo rezultira endotelnom disfunkcijom i ubrzanom apoptozom. Nešto brži srčani ritam nazoči u ovih bolesnika i tijekom dana.[1,3] Bolesnici imaju smanjenu varijabilnost srčanog ritma i povećanu varijabilnost arterijskog tlaka (AT). Uslijed nedostaka sna i posljedične hiperkatekolaminemije, OAS je praćena s inzulinskom rezistencijom, rezistencijom na leptin, povećanom aktivacijom trombocita i povećanim trombotskim rizikom.[1,2,4] Zbog forsirane inspiracije pri zatvorenom dišnom putu u bolesnika s OAS, posljedično pada intratorakalni tlak, čak do -65 mmHg. Ovaj se negativni tlak porenosi na atrije, ventrikule i aortu i remeti normalnu ventrikulsku funkciju.

OAS važan je čimbenik opasnosti javljanja brojnih kardiovaskularnih stanja i bolesti koje pokazuje *Tablica 1*.

to the decrease in oxygen saturation or with awaking.[1] The diagnosis of the obstructive sleep apnea (OSA) when the apnea-hypopnea index (AHI) is more then five per hour, with a pronounced sleepiness during the day. According to certain sources more then 85% of patients suffer from this disease in the US don't even know about it![2] Therefore, this percentage may be even higher in Croatia!?

Excessive sympathetic tone, repeated hypoxia stress, releases vasoconstrictor agents, primarily endothelin which triggers releasing inflammation mediators such as interleukin-6, plasmatic cytokine or the C-reactive protein. This results in an endothelial dysfunction and accelerated apoptosis. Somewhat faster heart rate is evident in these patients even during the day.[1,3] Patients have a decreased variability of the heart rhythm and an increased variability of the blood pressure (BP). Due to a lack of sleep and consequential hypercatecholaminemy, OSA is accompanied by the insulin resistance, resistance to leptin, increased activation of thrombocytes and an increased thrombotic risk.[1,2,4] Due to a forced inspiration at the time of closed respiratory tract in patients having sleep apnea, the intrathoracic pressure drops consequently even to -65 mmHg. This negative pressure is transferred to arteries, ventricles and the aorta and it disrupts the normal ventricular function.

Table 1. *The most common cardiovascular diseases in OSA patients.*

— hypertension
— heart failure
— myocardial infarction, ischemia
— stroke
— sudden cardiac death
— paroxysmal arterial fibrillation, atrial and ventricular ectopy
— AV conduction disorders (block type 2 or 3)
— malignant arrhythmia (ventricular tachycardia, fibrillation)

Arterijska hipertenzija. OAS i arterijska hipertenzija (AH) su često pridružene. Tako, 50% bolesnika s OAS ima AH, a 30% hipertoničara ima, često neprepoznatu OAS. Među hipertoničarima bez noćnog pada AT (tzv. nondiperima) često postoji i OAS.[5] OAS je neovisni čimbenik opasnosti za razvoj AH. Primjenom tzv. CPAP-uređaja (od engl. *Continuous Positive Airway Pressure*) postupno se normalizira AT i simpatički tonus tijekom sna. Postoje, dokazi da neki antihipertenzivi (klonidin, npr.) može smanjiti broj apneja u snu, dok cilazipril može smanjiti AT tijekom noći, a celiprolol tijekom dana u bolesnika s OAS.[3]

Zatajivanje srca. OAS se javlja u širokom rasponu od 10% do 50% bolesnika sa sistoličkim zatajivanjem srca![3] Upravo kombinacija hipoksije i AH u bolesnika s OAS, sinergistički, stimulira hipertrofiju klijetki pa posredno i nastanak zatajivanja srca. OAS dovodi do strukturnih i funkcijskih oštećenja srca i povoljnog terapijskog učinka CPAP-uređaja. Pad intratorakalnog tlaka (čak za 65 mmHg), prenosi se, uz zatvoreni ždrijelni dio dišnog puta, na ventrikule i uzrokuje tlačno opterećenje, pad udarnog volumena, povećanu simpatičku stimulaciju. Imajući na umu da se događa, ponekad i stotinama puta tijekom sna, jasno je da se postupno razvija ishemija, ventrikulska dilatacija i

OSA is an important factor of developing a number of cardiovascular conditions and diseases presented in *Table 1*.

Hypertension. OSA and hypertension are often associated. So, 50% of OSA patients have hypertension, and 30% of hypertensive patients often have an unrecognized OSA. Among the hypertensive without the normal nocturnal fall of BP (so called non-dippers) OSA is also often present.[5] OSA is an independent factor in developing hypertension. Using the CPAP device (Continuous Positive Airway Pressure) BP and the sympathetic tone are gradually normalized during sleep. There is evidence that some antihypertensive agents (e.g. clonidine) can decrease the number of apneas during sleep in OSA patients, while cilazipril can decrease the BP during a night and celipropol during a day.[3]

Heart failure. OSA occurs in a wide range from 10% to 50% of patients with systolic heart failure![3] It is the combination of hypoxia and hypertension in OSA patients, synergistically stimulating the ventricular hypertrophy and directly the occurrence of heart failure. OSA leads to structural and functional heart damage and favorable therapeutic effect of the CPAP device. The drop in intrathoracic

naposlijetku, njena disfunkcija![6,7] Kontinuirana primjena pozitivnog tlaka koji otvara dišne putove (CPAP-uređaja) smanjuje hipoksiju, AT i smrtnost u dekompenziranih kardiopata![8]

Cerebrovaskularni inzult. Blaga ili umjerena OAS javlja se u čak 40%-60% bolesnika s prolaznim ishemijskim napadajem.[9] Povećani rizik moždanog udara u bolesnika s OAS, uzrokovan je oscilacijama AT, smanjenim moždanim protokom, oštećenom cerebralnom autoregulacijom, endotelnom disfunkcijom te protrombotskim, upalnim stanjem. Postoje podaci da se u 25% bolesnika s umjerenom ili teškom OAS, javljaju nijemi moždani udari![9] CPAP-uređaj nudi bolesnicima nakon možadnog udara, povoljniju rehabilitaciju i bolju progonozu. Upravo je njima od neprocjenjive koristi adekvatna ventilacija, bez hipoksičnih epizoda koje mogu dodatno oštetiti mozak.[3] Neposredno nakon moždanog udara češća je CAS, od OAS, a u kroničnoj fazi češća je OAS.

Aritmije. Javljaju se u gotovo svakog drugog bolesnika s OAS.[10] Najčešće poremetnje ritma su atrijska fibrilacija, nepostojana ventrikulska tahikardija (VT), sinusni zastoj, AV blok 2. stupnja i česte ventrikulske ekstrasistole (više od 2/minuti). Aritmije se javljaju dva do četiri puta češće u bolesnika s OAS, posebice često se javlja paroksizmalna atrijska fibrilacija, nepostojana VT i ventrikulska ektopija.[3,10] Europsko multicentrično polisomnografsko ispitivanje pokazalo je 59%-tnu učestalost OAS u bolesnika s trajnom elektrostimulacijom srca te u 68% bolesnika s jednim AV blokom![11] Autori se zalažu za ispitivanje na OAS svih bolesnika koji su nositelji elektrostimulatora, zbog njenog potencijalno štetnog učinka na kardiovaskularni sustav! Izgleda da 50% bolesnika koji se podvrgava elektrokardioverziji boluje od OAS za razliku od 30%-tne učestalosti ove bolesti u ostaloj kardiološkoj populaciji bolesnika![10]

Ishemija, infarkt miokarda. Postoje nedvojbeni dokazi češćeg javljanja koronarne bolesti srca i rane koronarne smrtnosti u bolesnika s OAS nego u ostalih bolesnika. Bolesnici s OAS koji umru iznenada, najčešće umiru u snu između 22 sata i 6 sati ujutro, za razliku od ostalih bolesnika koji umiru iznenada najčešće u ranim jutarnjim satima, između 6 i 11 sati.[3] Ovo nedvojbeno upućuje na OAS kao akutni okidač ishemije miokarda sa svim njenim posljedicama. Adekvatno liječenje bolesnika s OAS primjenom CPAP-uređaja, značajno smanjuje mogućnost nastanka ishemije ili infarkta miokarda.[12] Uslijed hipoksije s hiperkapnijom u snu, u manjem postoku (u svakog petog ili šestog) bolesnika s OAS, javlja se plućna arterijska hipertenzija, ponekad i kronična opstrukcijska plućna bolest. OAS, mehanizmom povećane simpatičke stimulacije, uz AH, može pogoršati zatajivanje bubrega. Gotovo svaki drugi bolesnik u terminalnom stanju zatajivanja bubrega ima apneju u snu!

Liječenje. Budući da su bolesnici s OAS često pretile osobe, smanjenje tjelesne težine može značajno smanjiti simptome. Glavni način liječenja primjena je već spomenutog uređaja s kontinuirano-pozitivnim tlakom u dišnim putovima (tzv. CPAP-om) koji, otvara kolabirane dišne putove, u trenucima apneje.[13] Mandibularni "podizač" (od engl. *mandibular advancement*) u potpunosti sprječava hrkanje, ali OAS liječi tek u svakog drugog bolesnika (u onih s blažom OAS, AHI < 10).[3,13] Kirurški zahvati su obično "mutilirajući" (postavljanje traheostome ili uvulopalato-

pressure (even by 65 mmHg), is transferred along the closed laryngeal part of the airway, to ventricles causing pressure load, drop of stroke volume, increased sympathetic stimulation. Considering this, sometimes even for hundreds of times during sleep it is clear that ischemia and ventricular dilatation gradually develop eventually resulting in its dysfunction![6,7] Continuous application of positive pressure which opens the airways (CPAP devices) decreases hypoxia, BP and mortality in decompensated cardiac patients![8]

Stroke. Mild or moderate OSA develops in 40%-60% of patients with a transient ischemic attack.[9] Increased risk of stroke in OSA patients is caused by oscillations in BP, decreased cerebral flow, damaged cerebral self-regulation, endothelial dysfunction and a prothrombotic state inflammatory condition. There is data showing that 25% of patients with moderate or severe OSA have silent strokes![9] CPAP-device offers to patients beneficial rehabilitation and a better prognosis after the stroke. Those are the patients that benefit the most from adequate ventilation, without hypoxia episodes which may additionally damage the brain.[3] Immediately following the stroke CAS is more common than OAS, and in chronic phase OSA is more frequent.

Arrhythmia. It occurs in almost every second OSA patient.[10] The most common rhythm disorders are atrial fibrillation, inconsistent ventricular tachycardia (VT), sinus block, AV block type 2 and frequent ventricular ectopic beats (more then 2/minute). Arrhythmias occur two to four times more often in OSA patients, especially the paroxysmal atrial fibrillation, inconsistent VT and ventricular ectopy.[3,10] The European Multicenter Polysomnographic Study has shown a 59% occurrence of OSA in patients with permanent electrostimulation of the heart and in 68% of patients with one AV block.[11] Authors advocate studies on all OSA patients who have pacemakers because of its potentially harmful effect on the cardiovascular system! 50% of patients seem to undergo electrocardioversion suffer from OSA unlike 30% occurrence of this disease in the remaining cardiac patients![10]

Ischemia, myocardial infarction. There is undoubted evidence that the coronary heart disease and early coronary mortality occur more often in OSA patients than in some other patients. OSA patients, who suddenly die, most often die in sleep, between 10 p.m. and 6 a.m., unlike some other patients who most often die in the early morning hours between 6 and 11 a.m.[3] This undoubtedly indicates that OSA is an acute trigger of myocardial ischemia and all its consequences. An appropriate treatment of OSA patients with CPAP-devices, significantly decreases the possibility of ischemia or the myocardial infarction.[12] Due to sleep hypoxia with hypercapnia, a smaller percentage (every fifth or sixth) of OSA patient develops pulmonary hypertension, and sometimes chronic obstructive pulmonary disease. OSA, along with AH, may worsen the renal failure due to an increased sympathetic stimulation. Almost every second patient in terminal state of renal failure has sleep apnea!

Treatment. Since OSA patients are often obese, the loss of weight may significantly reduce the symptoms. The primary treatment is the application of aforementioned device with a continuous positive airway pressure which opens collapsed airways in moments of apnea.[13] Mandibular Advancement Device completely prevents snoring, but cures

faringoplastika), izvode se iznimno zbog čega su uglavnom napušteni.

Zaključno se može reći da bi na ovu razmjerno čestu, potencijalnu opasnu bolest trebali misliti u svih adipoznih bolesnika, koji hrču u snu, preko dana su pospani, a koji imaju jednu od nabrojenih kardiovaskularnih bolesti. Samo rano prepoznavanje i adekvatno liječenje može značajno smanjiti kardiovaskularni pobol i smrtnost.

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OSA only in every second patient (in those with milder sleep apnea, AHI < 10).[3,13] Surgical operations are usually "mutilating" (inserting a tracheostomy tube or an uvulopalatopharyngoplasty) and are performed as an exception and are mainly abandoned.

To conclude, we can say that we should consider this relatively frequent and potentially dangerous disease in all adipose patients who snore in their sleep, are sleepy during the day and have one of the mentioned cardiovascular diseases. Only early recognition and adequate treatment can significantly reduce the cardiovascular diseases and mortality.

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